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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/543,371	04/04/2000	Raghuram Kalluri	1440.1027005	6148

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HADDAD, MAHER M

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1644

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26

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/543,371	KALLURI, RAGHURAM
	Examiner Maher M. Haddad	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 11 September 2002 and 11 April 2003.

2a) This action is **FINAL**.                            2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-4 and 9 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-4 and 9 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>19</u> .	6) <input type="checkbox"/> Other: _____

## DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Maher Haddad, Art Unit 1644, Technology Center 1600.

2. Claims 1-4 and 9 are pending and currently under consideration.

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/11/02 and 4/11/03 has been entered.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

5. Claims 1-4 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is indefinite in the recitation "comprising a non-Goodpasture fragment of  $\alpha$ 3(IV) NC1 domain and comprising amino acid residues 185-203 of SEQ ID NO: 10", lines 1-2 because it is unclear whether the composition comprises one fragment or two fragments of  $\alpha$ 3(IV) NC1 domain.

B. Claim 9 is indefinite in the recitation of "amino acid residue 245 of SEQ ID NO:10", line 2, however SEQ ID NO:10 has only 244 amino acid residues.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

7. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed. *This is a New Matter rejection.*

The phrase "amino acid residue 180 to amino acid residue 245 of SEQ ID NO:10" claimed in claim 9, line 2 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 9/11/02 points to the specification for support for the newly added limitations "amino acid residue 180 to amino acid residue 245 of SEQ ID NO:10 as claimed in claim 9. However, the specification does not provide a clear support of "amino acid residue 180 to amino acid residue 245 of SEQ ID NO:10", Table 2, page 125 refers to Tum-4 fragment as residues 181-244. The instant claim now recited limitations which were not clearly disclosed in the specification and claims as originally filed.

8. Claims 1-4, and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a non-Goodpasture fragment of  $\alpha$ 3(IV) NC1 domain consisting of amino acid residues 185-203 of SEQ ID NO: 10, having at least one of the following activities (a) the ability to bind  $\alpha$ v $\beta$ 3 integrin, and the ability to inhibit proliferation of melanoma cells in vitro, wherein the ability to bind  $\alpha$ v $\beta$ 3 integrin is RGD-independent, an isolated fragment of  $\alpha$ 3(IV) NC1 domain, consisting of the amino acid sequence of amino acid residues 53-123 of SEQ ID NO:10, an isolated fragment of  $\alpha$ 3(IV) NC1 domain, consisting of the amino acid sequence of amino acid residues 181-244 of SEQ ID NO:10, does not reasonably provide enablement for a composition a non-Goodpasture fragment of  $\alpha$ 3(IV) NC1 domain and "comprising" amino acid residues 15 of SEQ ID NO:10, having at least one of the following activities (a) an ability to bind  $\alpha$ v $\beta$ 3 integrin and (b) an ability to inhibit proliferation of tumor cells *in vivo*, and a pharmaceutically-acceptable carrier in claims 1, wherein the ability to bind  $\alpha$ v $\beta$ 3 integrin is RGD-independent in claim 2, wherein the tumor cells are melanoma cells in claim 3, an isolated fragment of  $\alpha$ 3(IV) NC1 domain, "having" the amino acid sequence of amino acid residue 53 to amino acid 123 of SEQ ID NO:10 in claim 4; an isolated fragment of  $\alpha$ 3(IV) NC1 domain, "having" the amino acid sequence of amino acid residue 180 to amino acid residue 245 of SEQ ID NO: 10 in claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The terms "comprising " and "having" in claims 1, 4 and 9 are open ended and extend the fragment of  $\alpha$ 3(IV) NC1 peptides to include additional unrecited amino acids out side amino acid residues 185-203, 53-123 and 180-245 SEQ ID NO: 10. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the inhibition of melanoma cells or  $\alpha$ v $\beta$ 3 binding and that the relationship between the fragment and its activity was not well understood. It would require an

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undue amount of experimentation for one of skill in the art to arrive at the breadth of claimed fragments of  $\alpha 3$ (IV) NC1. Without sufficient guidance, the changes which can be made in the structure of "fragments" and still provide inhibition of melanoma cell proliferation or  $\alpha v\beta 3$  binding ability is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Also, at issue is whether or not the claimed composition would function to inhibit proliferation of tumor cells *in vivo*. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for *in vivo* use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

The specification discloses the Tum-4 (fragment 181-244 of SEQ ID NO:10) inhibited WM-164 melanoma cells but failed to inhibit C-PAE endothelia cells (page 124, lines 15-20). Further, the specification on page 125, lines 25-30, discloses that Tum-4 was the only deletion mutation that decreased the viability of the WM-164 melanoma cells. The exemplification is drawn to inhibit adhesion of endothelia cells to plates coated with the tumstation deletion mutants (page 2126). In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide, it's still along way to product (Edgington Biotechnology 10:383-389, 1992, see entire document, particularly page 386, column 3, paragraph 4).

In support, Kogan et al. (*J. Biol. Chem.*, 1995) disclose that single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion/binding activity (see entire document, including the Discussion). On the basis of the disclosed apparent *in vitro* observation alone, applicant concludes that the scope of the peptides defined by sequences encompassed by the claimed invention can have biological activity to inhibit the adhesion of target cell to the substrate and be provided as pharmaceutical compositions to subjects including human to effectively inhibit adhesion.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. As stated in the previous office actions mailed on 06/05/01 and 3/12/02, the filling date of claims with limitation which include the  $\alpha 3$ (IV) NC1 domain of Collagen from amino acids 53-123 and 185-203, of claims 1-4, is deemed to be the filling date of the instant application, filed 4/4/00, as no support is found for the said polypeptide fragments in priority documents 60/126,175 , 60/089,689 or 09/335,224.

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Applicant's arguments, filed 9/11/02 (Paper No. 18), have been fully considered, but have not been found convincing.

Applicant argues that the Examiner has not presented evidence or reasoning as to why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by claims, that is, fragments of full-length proteins can have the same properties as their parent molecules, and given that exactly such fragments were presented in US. App. No. 09/335,224. Applicant further argues that the subdividing protein sequences and of testing the resulting peptides are well-known in the art, and Applicant used precisely such well-known methods to produce the fragments now claimed. The disclosures of the prior application would therefore "reasonably convey" to one of ordinary skill in the art that the properties described could be found in fragments of the full-length proteins.

However, to comply with the written description requirement of 35 U.S.C 112, first paragraph and to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. See MPEP § 2163 for examination guidelines pertaining to the written description requirement.

Applicant further argues that the situation in *Ruschig* is not in any way analogous to the present application. Applicant contends that In *Ruschig*, the majority of the choices in starting materials for synthesis of the claimed compound would not even have resulted in that compound, while the present application and the priority documents, set for the three proteins of finite length, where the proteins possessed a specific, readily-assayable property. Applicant further argues that unlike *Ruschig*, where there were no specific pointers to the claimed compound, Applicant clearly indicated that a number of the further subdivisions of each of the anti-angiogenic proteins were likely, expected even, to possess the same activity.

However, Applicant disclosed a 244 amino acid sequence with no blaze marks directing the skilled artisan to the particular claimed fragments. In particular, no support where found in the prior applications to picked a fragment with anti-tumor characteristic possessed by the SEQ ID NO:10, which would make the basis of claims that cover the fragments that has that anti-tumor characteristic for example. Therefore, one cannot disclose a forest in the original application and then later pick a tree out of the forest and say here is my invention, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.

Applicant argues that *Fujikawa* is not applicable to this application. Applicant argues that one of ordinary sill could easily isolate anti-angiogenic fragments of the overall proteins according to the guidance already provided in the priority applications. Applicant further argues that no additional guidance or characteristics are needed to isolate new anti-angiogenic fragments of the overall proteins.

However, the introduction of claim changes which involve narrowing the claims by introducing a specific core structure for anti-tumor which are not supported by the priority applications

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disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Applicant argues that the instant disclosure is not analogous to the facts of *Martin*, wherein *Martin* involved whether disclosure of a cable supported claims to a device made out of the cables. Applicant argues that the instant disclosure is to particular full-length proteins with a defined activity, and fragments of those proteins also possessing the activity. Applicant argues that this application is easily distinguished from these cases in that Applicant has disclosed specific proteins with an unusual property, noting that the same property was likely to reside in subdivisions of the proteins.

However, 112, first paragraph, requires that the disclosure relied on be adequately specific as to the claim limitations that characterize the fragments.

Applicant argues that with the examiner reasoning, Applicant would be prevented from protecting the fruits of his discovery and would be afforded only later priority dates for those same fragments. Applicant concluded that such reasoning gives free rein to copyists, and would discourage applicants from allowing publication of their applications, and encourage protection by secrecy, rather than patent.

However, Applicant must file a patent Application, which describes the best form of the invention to enable one skilled in the art to practice the invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

*(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.*

*The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).*

11. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by *Kalluri et al* (J Biol Chem. 271(15):9062-9068, 1996) (IDS Ref. No. AW).

*Kalluri et al* teach a composition in a serum comprising a non-Goodpasture fragment of  $\alpha$ 3(IV)NC1 domain wherein the fragment comprises amino acid residues 185-203 of SEQ ID

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NO:10, reference  $\alpha$ 3/n-26 and  $\alpha$ 3/n-26/c-36 fragments (see page 9066 and Figures 1 and 5 in particular). Serum is considered to be a pharmaceutically-acceptable carrier. Kalluri *et al* further teach a fragment of  $\alpha$ 3(IV) NC1 domain having the amino acid sequence of amino acid residue 53-123 of SEQ ID NO:10 (reference  $\alpha$ 3/n-26 fragment (see page 9066 and Figure 1 in particular). Finally, Kalluri *et al* teach a fragment of  $\alpha$ 3(IV)NC1 domain, having the amino acid sequence of amino acid residue 180-243 of SEQ ID NO:10, e.g., reference  $\alpha$ 3/n-26 and  $\alpha$ 3/n-26/c-36 fragments (see page 9066 and Figure 1 in particular).

While the prior art teachings may be silent as to the “the ability to bind  $\alpha$ v $\beta$ 3 integrin and the ability to inhibit proliferation of tumor cells” in “RGD-independent” binding per se; the reference product is the same as the claimed product. Therefore “the ability to bind  $\alpha$ v $\beta$ 3 integrin and the ability to inhibit proliferation of tumor cells” is considered inherent properties.

The terms “comprising” and “having” in instant claims 1 and 4 are open ended. They would open up the claim to include the reference  $\alpha$ 3/n-26 and  $\alpha$ 3/n-26/c-36 fragments.

Since the office does not have a laboratory to test the reference fragments, it is applicant’s burden to show that the reference fragments do not bind to the  $\alpha$ v $\beta$ 3 integrin is RGD independent and do not inhibit proliferation of melanoma tumor cells recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

Claim 9 will be reintroduced if the range of amino acid residues 180-243 is included.

The reference teachings anticipate the claimed invention.

12. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Han *et al* (J Biol Chem. 272(33):20395-20401, 1997) (IDS Ref. No. AT4).

Han *et al* teach a composition comprising a non-Goodpasture fragment of  $\alpha$ 3(IV) NC1 domain, wherein the fragment comprising amino acid residues 185-203 of SEQ ID NO:10 (see abstract, page 20395 and page 20396 under preparation of synthetic peptides, under production of monoclonal antibodies and under results and table 1 in particular). Han *et al* further teaches that the fragments not only promote adhesion of human melanoma cells but also inhibits their proliferation (see abstract in particular). Han et al teach the peptides in coating buffer (0.1 M Tris-HCL buffer, pH 7.5) (page 20396, under attachment assay in particular), which is considered a pharmaceutically-acceptable carrier.

The reference teachings anticipate the claimed invention.

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13. Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S Patent No. 5,973,120 (IDS Ref. No. AJ).

The '120 patent teaches a composition comprising a non-Goodpasture fragment of human  $\alpha$ 3(IV) NC1 domain, wherein the fragment comprises amino acid residues 185-203 of SEQ ID NO:10, reference SEQ ID NO:25 is a 218 amino acid sequence that is a fragment of claimed SEQ ID NO:10 (see col., 35-36, and referenced claim 3 in particular). The '120 patent teaches the in GP sera passed through  $\alpha$ 3 peptide packed column (see col., 4, Fig., 6) which place the  $\alpha$ 3 peptide in a composition. The '120 patent further teach a fragment of  $\alpha$ 3(IV) NC1 domain having the amino acid sequence of amino acid residue 53-123 of SEQ ID NO:10 (reference SEQ ID NO:25 fragment (see col., 35-36, and referenced claim 3 in particular). Finally, '120 patent teaches a fragment of  $\alpha$ 3(IV)NC1 domain, having the amino acid sequence of amino acid residue 180-243 of SEQ ID NO:10, e.g., reference col., 35-36, and referenced claim 3.

While the prior art teachings may be silent as to the “the ability to bind  $\alpha$ v $\beta$ 3 integrin and the ability to inhibit proliferation of tumor cells” in “RGD-independent” binding per se; the reference product is the same as the claimed product. Therefore “the ability to bind  $\alpha$ v $\beta$ 3 integrin and the ability to inhibit proliferation of tumor cells” is considered inherent properties.

The terms “comprising” and “having” in instant claims 1 and 4 are open ended. They would open up the claim to include the reference 218 amino acid fragment.

Since the office does not have a laboratory to test the reference fragment, it is applicant's burden to show that the reference fragments do not bind to the  $\alpha$ v $\beta$ 3 integrin is RGD independent and do not inhibit proliferation of melanoma tumor cells recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

Claim 9 will be reintroduced if the range of amino acid residues 180-243 is included.

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

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Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.  
Patent Examiner  
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June 30, 2003

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